

POLYENOLATES OF UNSATURATED CARBOXYLIC ACIDS IN SYNTHESIS. A STRAIGHTFORWARD SYNTHESIS OF RETINOIC ACIDS.

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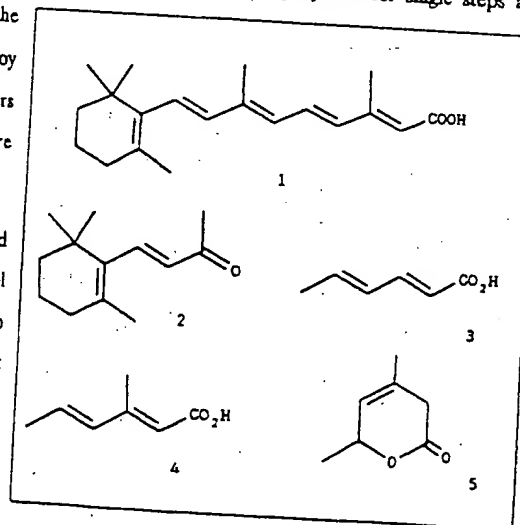
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SUMMARY. Retinoic acids are prepared in a two step procedure by addition of lithium trienediolates of sorbic acid and 3-methyl-sorbic acid to β -ionone.

The widespread and keen interest for retinoic acids is justified by their outstanding applications in Dermatology and Cosmetics¹.

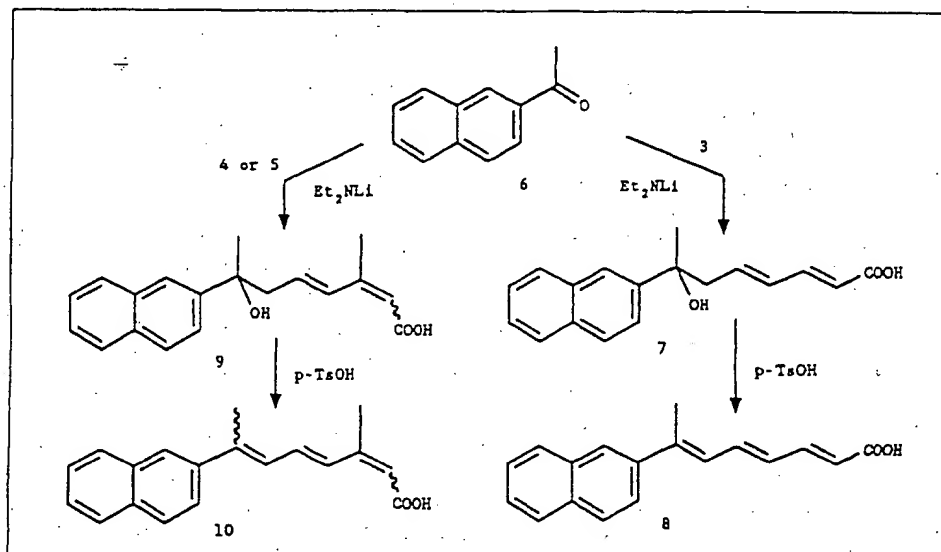
β -Ionone 2 is the obvious starting material for synthesis of retinoic acid 1 or of the modified retinoid acids which retain the cyclic end of the molecule. Thus, for a straightforward synthesis a C-7 carboxylic acid fragment should be added directly to β -ionone. However, in published synthetic procedures, β -ionone is first converted to C-10, or C-15 aldehydes, which then add a C-10 or a C-5 carboxylic derivative through Reformatsky, Wittig, or Wittig-Horner reactions². According to other recent methods, β -ionone is converted to C-15 phosphonium salts³⁻⁶ or sulfones⁷, which then react with the convenient C-5 aldehydes or halides. High yields for single steps are commonly reported, but final yields are limited by the number of steps. Aldol type reactions which employ unsaturated carboxylic acids or their esters as donors have been described as well, but again several steps are required^{8,9}.

We wish to report here that retinoic acid and modified retinoid acids can be easily prepared by aldol type addition of a d^6 carboxylic polyenolate to β -ionone. Although yields presently attained are not high, they are comparable, when not superior, to those described for most syntheses of retinoic acids.



Sorbic acid 3 had already been described as a d^6 synthon¹⁰, and thus could become a convenient building block for synthesis of nor-retinoids. (E,E)-3-Methylhexa-2,4-dienoic acid 4 or the 4,6-dimethyldihydropyrone 5, a precursor of the 2Z-isomer of acid 4, were similarly expected to be convenient for preparation of retinoic acids¹¹.

2-Acetonaphthone 6 was used as a simpler substrate for evaluation of the above d^6 synthons. Reaction of this ketone with the trienediolate of sorbic acid 3 and dehydration of the resulting hydroxy acid 7 with p-toluenesulfonic acid in dichloromethane afforded the all E 7-(2-naphthyl)-2,4,6-octa-trienoic acid 8, mp 214-215°C (MeOH) in 53%^{12,13}.

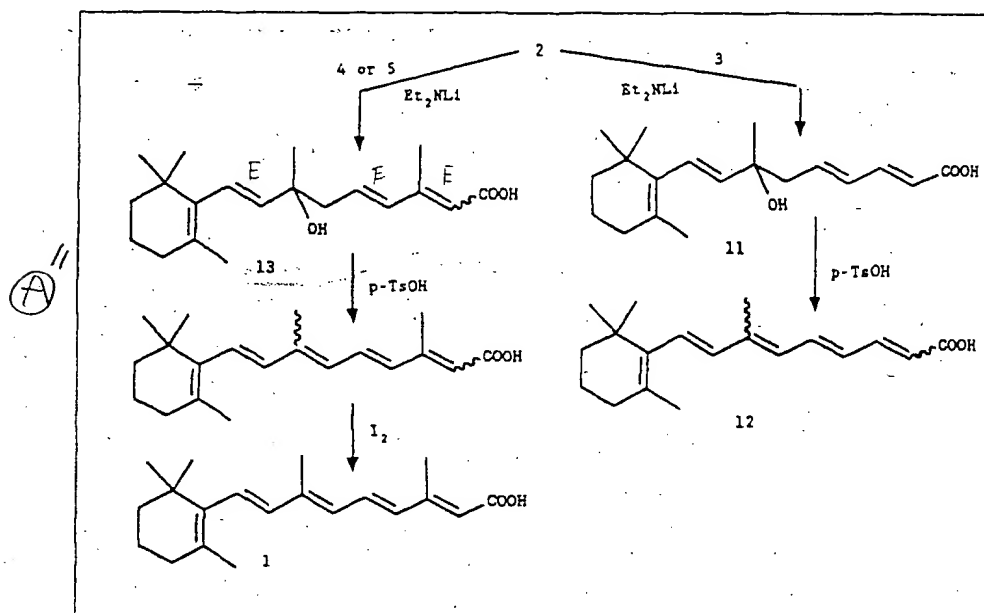


Methyl-sorbic acid 4 and dimethyldihydropyrone 5 were expected to lead to 2-E- and 2-Z-retinoid acids, respectively, but on reaction with the naphthyl ketone 6 they both gave the same 2-Z-hydroxy acid 9, along with a smaller amount of the 2E isomer in 51 and 34% yield respectively, after chromatographic purification. When 9 was dehydrated, the 3-methyl-7-(2-naphthyl)-2,4,6-octatrienoic acid 10¹⁴ was obtained in 95% yield, as a mixture of 2E and 2Z isomer¹³.

Reaction of sorbic acid trienediolate with unsaturated ketones is known to occur in a rather unpredictable way, and that mixtures of 1,2- and 1,4-addition products through the α , γ , or ω carbon atoms result, whose composition is subject to subtle structural features, as well as to reaction conditions¹⁰. Addition of this trienediolate to β -ionone 2 was simpler than first expected, and the resulting mixture contained the hydroxy acid 11, along with

smaller amounts of the corresponding 1,4- and 1,6- ω -adducts. Difficulties arose on purification, as a consequence of the poor chromatographic recovery of the 1,2-adduct 11, which was best obtained in 20% by flash chromatography. Dehydration of this acid gave in 90% the unstable 20-nor retinoic acid 12¹⁵ as an oil, whose ¹Hnmr spectrum showed to be a 6 E/Z mixture.

Similarly, reaction of methyl-sorbic acid 4 or dimethyl- dihydropyrone 5 with β -ionone gave the hydroxy acid 13 in 40 and 32% yields respectively, as a 4:6 2E:2Z mixture after purification by flash chromatography. Dehydration afforded in 95% yield a 2E/Z and 6E/Z mixture, from which all-E retinoic acid 1 crystallized¹⁶ after isomerization by iodine.



As isomerizations catalyzed by iodine³ or palladium salts^{5,17} are well known to lead to 2E or to 6E retinoids in high yields, we think that the present methodology affords an important new approach for the synthesis of retinoic acids and other retinoids¹⁸. We are presently improving and extending the method to other substrates.

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- 12.- As a typical procedure: Sorbic acid (1.01 g, 9 mmol) in THF (10 ml) was added slowly to a solution of lithium diethylamide [from naphthalene, lithium (0.14 g, 20 mmol of metal) and diethylamine] in THF (10 ml) at -70°C. The solution was stirred for 1 h at 0°C and cooled again at -70°C. 2-Acetonaphthone 6 in THF (10 ml) was added, and the solution stirred for 2 h at room temperature. Working up by addition of water, evaporation of the solvent, washing with ether, and acidification of the residue with dil HCl gave hydroxyacid 7 as an oil (2.18 g, 86%). This and p-toluenesulfonic acid (0.9 g) were heated under reflux for 20 min in CH₂Cl₂ (200 ml). The mixture was washed with water. Evaporation of the solvent gave crude acid 8 (1.83 g) which crystallized from methanol as yellow prisms (1.325 g, 53%) m.p. 214-215°C.
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